Sensitization to Cat Allergen Is Associated with Asthma in Older Men and Predicts New-onset Airway Hyperresponsiveness

The Normative Aging Study

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To explore the relationship between sensitization to inhalant allergens and adult asthma, we performed two nested case-control studies of men being followed in the VA Normative Aging Study. In Study A, 46 subjects (mean age, 61.2 ± 8.1 yr) with symptoms of asthma and an abnormal methacholine challenge test (cases) were compared with 92 age- and smoking-history-matched subjects, who denied symptoms and had normal methacholine challenge tests (controls). The age of onset of wheezing symptoms for the cases was 49.0 ± 15.7 yr. Serum IgE reactivity to the aeroallergens *Der p* 1 and 2, cat, ragweed, and mouse was compared in cases and controls. Cases were more likely to be sensitized to cat allergen (23.9% versus 4.4%, $p < 0.001$) than were controls. Prevalences of sensitization to *Der p* 1, *Der p* 2, ragweed, and mouse were low and similar in the two groups. In Study B, 33 cases who developed new onset airway hyperresponsiveness on methacholine challenge testing were compared with 66 age-matched controls who maintained normal methacholine challenge tests. Cases had a higher prevalence of serum IgE reactivity to cat allergen (18.2% versus 6.1%, $p = 0.059$) and *Der p* 2 (21.2% versus 10.6%, $p = 0.153$) measured in serum obtained 3 yr before the development of airway hyperresponsiveness. These results suggest that in older men, sensitization to cat allergen is associated with asthma and that sensitization predates airway hyperresponsiveness to methacholine. Litonjua AA, Sparrow D, Weiss ST, O'Connor GT, Long AA, Ohman JL, Jr. Sensitization to cat allergen is associated with asthma in older men and predicts new-onset airway hyperresponsiveness: the Normative Aging Study. AM J RESPIR CRIT CARE MED 1997;156:23–27.

Asthma in older adults is thought to differ from that in children and young adults (1, 2). Studies in children have suggested that atopy and exposure to common aeroallergens play a major role in the development of asthma (3–5). In the elderly asthmatic, however, the roles these factors play are thought to be less important than in children (3), probably because atopy and the allergic response are known to decrease with age. Despite the natural history of the allergic response, asthma has previously been shown to be associated with increased levels of IgE standardized for age and sex (6). It is nevertheless widely believed that asthma in the elderly is more commonly nonatopic. This belief may have implications in how practitioners manage the disease in this age group. Indeed, in published discussions about the management of asthma in the elderly population (7, 8), evaluation of sensitization to common aeroallergens and allergen avoidance have not been stressed as much as they have in children and younger adults.

We conducted two nested case-control studies to address the role of the allergic response to environmental aeroallergens in the development of asthma in a sample of older men from the Normative Aging Study. In the first case-control study, we investigated the cross-sectional association between prevalent cases of asthma and sensitization to four common aeroallergens in a sample of middle-aged to older men. In a second case-control study, we examined the association between sensitization to these common aeroallergens and new-onset airway hyperresponsiveness in another sample of men with similar ages.

METHODS

Population

The Normative Aging Study is a longitudinal study of aging established by the Veterans Administration in 1961, and it has been de-

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scribed elsewhere (9). Briefly, the study cohort consists of 2,280 community-dwelling men from the Greater Boston area, ranging in age from 21 to 80 yr on enrollment into the study. Volunteers were screened at entry according to specific health criteria (9) and were free of known chronic medical conditions, in particular, asthma, chronic bronchitis, and chronic sinusitis.

Since entry, volunteers have reported for periodic examinations, each consisting of a uniform medical history and physical examination, along with blood and urine tests and electrocardiography. Beginning in 1984, subjects have also been studied with a detailed respiratory symptom and smoking questionnaire, methacholine challenge test, allergy skin tests, and serum IgE measurements. Participation in this study has been approved by the Human Studies Subcommittee of the Research and Development Committee, Department of Veterans Affairs Outpatient Clinic, Boston, Massachusetts. Written, informed consent was obtained from all subjects.

Study Sample and Design

The subjects (cases and controls) for the current investigation were subgroups from the Normative Aging Study cohort. Two nested case-control studies were performed. The first cross-sectional study (Study A) consisted of 46 cases with prevalent symptoms of asthma (defined as a positive response to at least one of three wheeze questions from the ATS-DLD-78 questionnaire; *see* Questionnaire Data section) and abnormal methacholine challenge test results (see definition of abnormal methacholine challenge test below). Records of subjects who reported for their scheduled examination from May 1984 to August 1992 were reviewed chronologically, and cases were identified when their records first revealed both an abnormal methacholine test and asthma symptoms on the same examination. Two controls per case, matched for age (± 2 yr) and current smoking status (current smoker versus current nonsmoker) were identified from those who reported for their scheduled examination during the same period. Controls answered negatively to all three wheeze questions and had negative results on methacholine challenge testing, as defined below.

For the second study (Study B), 33 cases who exhibited new onset airway hyperresponsiveness to methacholine during follow-up (May 1984 to August 1992) were identified and compared with 66 age-matched (± 1 yr) controls whose methacholine challenge tests remained negative. Subjects who were chosen as controls in Study A were allowed to be subjects for Study B. Cases were identified as those subjects with a positive methacholine challenge test during a scheduled examination (designated as the "index" examination) and with a negative methacholine challenge test on a previous examination. Controls, on the other hand, were selected from those with two negative methacholine tests from two consecutive examinations, the latter examination corresponding to the case's index examination.

Questionnaire Data

A questionnaire (ATS-DLD-78) was administered to each participant to obtain information on smoking habits, respiratory symptoms, and illness (10). For Study A, cases of asthma were defined as subjects who gave a positive response to one or more of the following three questions. (*1*) "Do you wheeze occasionally apart from colds?" (*2*) "Do you wheeze most days or nights?" (*3*) "Have you ever had an attack of wheezing that has made you feel short of breath?" Controls answered negatively to all three wheeze questions.

For both Study A and Study B, the age when wheezing began was calculated by analyzing the subquestions of the three wheeze questions above. For subjects who answered positively to either of the first two wheeze questions, the subquestion was: "For how many years has this been present?" For subjects who answered positively to the third wheeze question, the subquestion was: "How old were you when you had your first such attack?" If discrepancies arose for the age at first wheeze, the age taken from the third wheeze question and its subquestion was used in the analysis.

Spirometry and Methacholine Challenge Protocol

Spirometry and methacholine challenge protocol were performed as previously reported (11, 12). Subjects underwent a methacholine challenge protocol adapted from that of Chatham and colleagues (13). Saline and methacholine solutions were aerosolized using a DeVilbiss 646 nebulizer attached to a DeVilbiss air compressor (DeVilbiss, Somerset, PA). All inhalations were 6-s inspiratory maneuvers from residual volume to total lung capacity, followed by 2 s of breathholding. Incremental doses of methacholine were inhaled at 5-min intervals according to the following schedule: five inhalations of 0 mg/ml (phenol-buffered saline alone), one inhalation of 1 mg/ml, one inhalation of 5 mg/ml, four inhalations of 5 mg/ml, one inhalation of 25 mg/ml, and four inhalations of 25 mg/ml. Previous determination of nebulizer output by weight (11) indicated that the methacholine inhalation schedule corresponded to the following cumulative doses of methacholine in micromoles: 0, 0.330, 1.98, 8.58, 16.8, and 49.8. Spirometry was performed 30, 90, and 180 s after each inhalation level. If the first two spirograms at each level were consistent (FEV_1 within 5%), then the higher measurement of these two was chosen for analysis. Otherwise, the higher FEV_1 measurement from the most consistent pair of acceptable spirograms was used. The test was terminated when a 20% decline in FEV_1 from the postsaline value occurred, or at the end of the dose schedule if such a decline did not occur.

For both Study A and Study B, the methacholine test was defined as positive when a 20% or greater decline in FEV_1 from the postsaline value occurred at one inhalation of 1 mg/ml methacholine solution through four inhalations of 5 mg/ml (corresponding to a maximal cumulative methacholine dose of 8.58 mg/ml). For Study A, controls were identified from subjects who did not exhibit a 20% or greater decline in FEV_1 throughout the entire methacholine challenge test protocol (negative methacholine challenge test). In order to obtain sufficient numbers for Study B, a negative methacholine test among cases and controls was defined as the absence of a 20% or greater decline in FEV_1 at one inhalation of 1 mg/ml methacholine solution through four inhalations of 5 mg/ml.

Measurement of IgE Antibody

For Study A, samples of serum from cases and controls were obtained at the time of the scheduled examination and then frozen at −20° C until assays were performed. For Study B, stored, frozen samples collected from cases and controls 3 yr before the index examination were used.

IgE antibodies to ragweed and mouse antigen were measured using an ELISA assay as described in a previous report (14). Briefly, 25-μg/ml concentrations of ragweed antigen and purified mouse allergen (*Mus m* 1) were applied to microtiter plates and followed by incubation with dilutions of human serum. After successive applications of antihuman IgE and color-developing reagent, optical densities of the wells containing standard dilutions of a positive control were used to compute the lower limit of sensitivity of the assay, which was typically 6 to 10 SD above values representing the lower flat portion of the standard curve.

The minimum value considered to be significantly positive for each IgE antibody (ragweed and mouse) was defined separately in each study by using the control group's mean and SD (follow-up values only for Study B). More than 2 SD above the mean was taken as significantly positive. The mean of the control group for each antigen fell above the lower end of the linear portion of the standard curve.

Measurement of specific IgE antibody to cat (*Fel d* 1) and dust mite (*Der p* 1 and *Der p* 2) antigens was performed at an outside laboratory (ImmuLogic Pharmaceutical Corporation) according to a somewhat different ELISA assay protocol. Dynatech Immulon II (Dynatech Laboratories, Inc., Chantilly, VA) plates were coated for 4 to 6 h at room temperature with 100 μl each of *Fel D* 1 antigen (diluted to 1 μg/ml concentration with phosphate-buffered saline, PBS) and *Der p* 1 and *Der p* 2 antigens (both diluted to 5 μg/ml concentrations with PBS). One hundred microliters of human serum dilutions were added to the plates in duplicate. At least one reference serum well containing detectable IgE levels to each of the allergens and four blank wells (no serum, PBS only) were run on each plate along with serum dilutions from subjects. After application of biotinylated goat antihuman IgE (KPL cat no. 16-10-04) and color-developing reagent, absorbance was read at 490 to 492 nm.

The resultant optical density (O.D.) values were averaged for each dilution and the average blank value obtained from wells incubated without serum was subtracted. A serum sample was considered positive for IgE for a specific antigen if a blank-subtracted O.D. value ≥ 0.3 was obtained on at least one serum dilution.

TABLE 1

SUBJECT CHARACTERISTICS OF STUDY A

Characteristics	Subjects with Asthma ($n = 46$)	Control Subjects ($n = 92$)	p Value
Age, yr*	61.2 (8.1)	61.1 (8.0)	0.994
Smoking status†			
Current smokers	13 (28.3)	26 (28.3)	0.478
Current nonsmokers	33 (71.7)	66 (71.7)	
Pulmonary function, % pred*			
All subjects			
FEV_1	80.2 (14.6)	96.7 (14.1)	< 0.0001
FVC	91.8 (13.1)	99.6 (14.1)	0.002
Current smokers			
FEV_1	72.1 (9.0)	93.3 (14.7)	< 0.0001
FVC	88.6 (12.4)	99.8 (14.7)	0.024
Current nonsmokers			
FEV_1	83.4 (15.2)	98.0 (13.7)	< 0.0001
FVC	93.1 (13.4)	99.6 (13.9)	0.030

* Values are means, with SD shown in parentheses.
† Number of smokers, with percentages shown in parentheses.

TABLE 3

SUBJECT CHARACTERISTICS OF STUDY B

Characteristics	Subjects who Developed Airway Hyperresponsiveness ($n = 33$)	Control Subjects ($n = 66$)	p Value
Age, yr*	61.3 (6.7)	61.3 (6.8)	0.967
Smoking status†			
Current smokers	7 (21.2)	13 (19.7)	0.363
Current nonsmokers	26 (78.8)	53 (80.3)	
Pulmonary function, %*			
All subjects			
FEV_1	87.4 (15.0)	98.7 (12.5)	0.0001
FVC	93.0 (15.4)	100.3 (14.2)	0.021
Current smokers			
FEV_1	81.3 (15.8)	91.6 (16.0)	0.183
FVC	93.0 (17.0)	96.6 (18.6)	0.678
Current nonsmokers			
FEV_1	89.0 (14.6)	100.4 (10.9)	0.0002
FVC	93.0 (15.2)	101.2 (13.0)	0.015

* Values are means, with SD shown in parentheses.
† Number of smokers, with percentages shown in parentheses.

Statistical Analysis

Statistical analyses were conducted using independent *t* tests and chi-square tests. Stratified analyses were carried out in each study, and appropriate chi-square tests were performed on proportions. Conditional logistic regression was performed using the NLIN procedure in SAS (15). All analyses were performed with the SAS statistical software package (SAS Institute, Inc., Cary, NC).

RESULTS

Study A

Baseline characteristics of the 46 cases and 92 controls are shown in Table 1. Pulmonary function test results (mean of percent predicted) were significantly lower in cases than in controls. These differences remained significant even after stratifying for current smoking status (Table 1). Among the 46 cases, six (13.0%) responded affirmatively to all three wheeze questions, 22 (47.8%) responded affirmatively to two wheeze questions, and 18 (39.1%) responded affirmatively to one wheeze question. Subquestions to these items revealed that the mean age of reported onset of wheezing symptoms was 49.0 ± 15.7 yr, with a range of 5 to 78 yr.

Serum IgE reactivity to the aeroallergens *Der p* 1 and 2, cat, ragweed, and mouse was compared between cases and controls (Table 2). Cases with asthma were significantly more likely to have positive IgE binding to cat antigen than were controls (23.9% versus 4.4%, $p < 0.001$). In a logistic regression model taking the matching factors of age and smoking into account and controlling for baseline lung function, the odds ratio for having asthma was 4.10 (95% CI = 1.05–16.00) among subjects with positive IgE binding to cat antigen. Prevalence of IgE binding to *Der p* 1, *Der p* 2, ragweed, and mouse antigens were low and similar among cases and controls.

Study B

Baseline characteristics of the 33 cases who developed new-onset airway hyperresponsiveness and their age-matched controls are presented in Table 3. Pulmonary function testing results showed lower values for the cases with new-onset airway hyperresponsiveness than for the controls. This difference persisted among current nonsmokers. However, among current smokers, this difference was not statistically significant (Table 3).

The prevalence of positive IgE binding to allergens in sera obtained 3 yr before the development of airway hyperresponsiveness in cases is shown in Table 4. Cases with new-onset airway hyperresponsiveness were more likely to have had positive serum IgE binding to cat allergen than were controls (18.2% versus 6.1%, $p = 0.059$) 3 yr before the development of airway hyperresponsiveness. These cases also had a higher prevalence of positive IgE binding to *Der p* 2 than did controls (21.2% versus 10.6%, $p = 0.153$), although this difference was not statistically significant. In a conditional logistic regression model accounting for matching on age and controlling for current

TABLE 2

IgE BINDING TO ALLERGENS (PERCENT POSITIVE), STUDY A

	Subjects with Asthma ($n = 46$)	Control Subjects ($n = 92$)	p Value
Dust mite*			
Der p 1	8.7	8.7	1.0
Der p 2	19.6	12.0	0.231
Cat*	23.9	4.4	< 0.001
Ragweed†	4.4	5.4	0.784
Mouse†	4.4	4.4	1.000

* A serum sample was considered positive for IgE for these allergens if a blank-subtracted O.D. value of 0.300 or greater was obtained for any serum dilution.
† An IgE value was considered positive for these allergens if it was greater than 2 SD above the mean value for the control group.

TABLE 4

IgE BINDING TO ALLERGENS (PERCENT POSITIVE), STUDY B

	Subjects who Developed Airway Hyperresponsiveness ($n = 33$)	Control Subjects ($n = 66$)	p Value
Dust mite*			
Der p 1	12.1	7.6	0.458
Der p 2	21.2	10.6	0.153
Cat*	18.2	6.1	0.059
Ragweed†	3.0	6.1	0.516
Mouse†	6.1	4.6	0.746

* A serum sample was considered positive for IgE for these allergens if a blank-subtracted O.D. value of 0.300 or greater was obtained for any serum dilution.
† An IgE value was considered positive for these allergens if it was greater than 2 SD above the mean value for the control group.

smoking status and baseline lung function, subjects with positive IgE binding to cat allergen were five times more likely to have asthma than were subjects without positive IgE binding to cat allergen (OR = 5.09, 95% CI = 1.20–21.59).

There was no difference in the prevalence of wheezing symptoms between cases who exhibited new-onset airway hyperresponsiveness and their controls on the examination preceding the index examination: four (12.1%) of 33 cases and eight (12.1%) of 66 controls. In contrast, when asked at the time of the index examination (first examination with positive methacholine challenge test for the cases), eight (24.2%) of 33 cases reported wheeze symptoms compared with only six (9.1%) of the 66 controls ($p < 0.05$). Furthermore, these eight cases had a mean age at reported onset of wheeze symptoms of 50.9 ± 13.0 yr, and all but one reported an age of onset after 45 yr.

DISCUSSION

The results of our first case-control study (Study A) show a significant association between sensitization to cats and the presence of asthma in the group of older men. The identification of subjects with asthma in epidemiologic studies has been problematic because of a lack of a common definition. In a majority of the studies of asthma in the elderly, the predominant symptom reported is wheeze (7). Because airway hyperresponsiveness is central in the clinical definition of asthma, cases of asthma were identified as those subjects who had both wheezing and airway hyperresponsiveness. A similar definition of asthma was used recently in a study of asthma in children (16).

We were able to identify 46 cases who fit this definition of asthma. Of these, 19 (41.3%) reported a doctor's diagnosis of asthma, 13 (28.2%) reported taking any asthma medication in the previous year, and only six (13.0%) were receiving regular medications. Thus, it appears that this group of cases is composed of subjects with generally mild asthma. This is not surprising since subjects were drawn from the general population, in contrast to those with more severe asthma who would be seen in a clinical setting.

Asthma is known to be a heterogeneous condition. It can begin in childhood and run a chronic, relapsing course; or it can become quiescent with many asymptomatic years, only to recur later in life, or it can be first recognized in the later stages of life. Our sample of older asthmatics in Study A appears to reflect this variable age of onset. The mean age at onset of wheezing symptoms among these cases was 48 ± 16.8 yr. Twenty-eight (63.6%) of the cases had their onset of wheeze symptoms before the age of 60 and 16 (36.4%) after the age of 60. This variable age at onset of adult asthma is very similar to findings in two previous studies on asthma in the elderly (2, 17), where asthma was defined as doctor-diagnosed asthma and as self-reported asthma, respectively.

Exposure and sensitization to common aeroallergens have received significant attention as risk factors for asthma. The majority of studies, which focus on the role of these factors in the development of asthma in infants and children (5), have shown that exposure and sensitization to dust mites is an important factor associated with asthma. However, other common aeroallergens were also found to have significant associations with asthma. In fact, in a mite-free environment, sensitization to cat and dog allergens has recently been shown to have a significant association with asthma in children (4). In that study, 67 and 62% of children with asthma had IgE antibodies to dog and cat, respectively. In adults, elevated IgE has also been associated with asthma. Burrows and colleagues (17) found that the mean IgE of elderly asthmatics was significantly elevated compared with that of nonasthmatic subjects of the same age and sex. In another sample from the Normative Aging Study, Ohman and colleagues (14) showed a significant association between new-onset wheezing and IgE binding to dust mite antigen. This study also showed a trend for increased IgE binding to both cat and ragweed among subjects with new-onset wheezing, although not statistically significant. Our results are consistent with previous findings in that sensitization to common aeroallergens, in this case cat allergen, is significantly associated with asthma. Sensitization to dust mite antigen was also more common among asthmatics than among control subjects, although the association was not as strong as that for cat antigen (Table 2). Kalliel and colleagues (18) reported on 72 consecutive adult asthmatic patients from their clinic; 42 of the adult asthmatics were atopic, and the most frequent blood test for specific IgE (FAST) was cat (62%), followed by dog (36%) and dust mite (31%). The prevalence of sensitization in our sample of older men is not as high as that for studies in children and is consistent with the knowledge that sensitization to inhaled allergens wanes with age (19, 20).

Although Study A showed the relation of sensitization to aeroallergen and asthma, we wanted to know if sensitization could predict the later appearance of asthma. Because it is very difficult to pinpoint the beginning of the clinical syndrome, we decided to investigate the association of prior sensitization to the onset of airway hyperresponsiveness. Results from Study B show that sensitization to common aeroallergens predicts the appearance of airway hyperresponsiveness 3 yr later.

Airway hyperresponsiveness is known to be a risk factor for asthma. Studies by Hopp and colleagues (21) and Zhong and coworkers (22) have recently shown that airway hyperresponsiveness to methacholine precedes the recognition of clinical asthma. In our sample of cases and controls for Study B, the prevalence of wheezing symptoms between both groups was identical on the examination preceding the index examination. In contrast, at the time of the index examination, the prevalence of wheezing symptoms among the cases with new-onset hyperresponsiveness was significantly greater than that among the controls, suggesting that subjects were beginning to experience symptoms along with the new-onset airway hyperresponsiveness. One previous study by Burrows and colleagues (17) found that symptoms suggesting asthma are usually present for many years before the disease is diagnosed in elderly subjects.

The role of exposure to aeroallergens in the development of asthma in children and young adults is clear. In many areas, sensitization to the house dust mite appears to have the most important association with asthma (5); however, other aeroallergens may also be equally important (4). Exposure to aeroallergens may also be an important risk factor for some adults who develop asthma at a later age. Although IgE antibodies to dust mites were detected more frequently among the cases in this study than among the controls, the association was not as strong as that for antibody to cat. It was previously shown in a cohort of young adult asthmatics that the cumulative duration of exposure to domestic animals is a significant determinant of sensitization to animal-derived antigens (23), and this mechanism may very well apply to the older men in our study.

Several limitations are apparent in our study. Because subjects were screened for chronic diseases (including asthma) on entry into the study, we were able to identify only 46 subjects who satisfied our definition for asthma in Study A. Since methacholine challenge testing began in 1984, only 33 subjects with new-onset airway hyperresponsiveness were identified for Study B. The small sample size limits the power of our study and may explain why we did not obtain statistical significance for the differences between groups with regard to sensi-

tization to the other aeroallergens, in particular, to dust mites. Another limitation of our work is the lack of prospective data collection, particularly in Study A. Ideally, etiologic research is best conducted by prospective collection of risk-factor data before the onset of disease. Longitudinal data were collected in Study B, although case status was ascertained before IgE antibodies were measured. Nevertheless, laboratory personnel were unaware of case status at the time of the antibody measurement. We also lacked information about the environment to which our cohort was exposed. Thus, any question regarding allergen burden in relation to sensitization cannot be answered by our study. These limitations, however, should not affect the validity of our results. In addition, our findings are consistent with results from other studies on younger groups of subjects.

In conclusion, we have shown that in this sample of older men, sensitization to cat allergen is significantly associated with the presence of asthma. Furthermore, sensitization to cat allergen may play a role in late-onset asthma since it predicted the development of airway hyperresponsiveness in this sample of older men. Although we did not measure IgE levels to other common aeroallergens such as dog and cockroach, it is likely that these also play a role depending on the intensity and duration of exposure. Our study, in addition to the other studies cited, supports the strong association between sensitization to common aeroallergens and asthma. It is likely that the important allergens that cause sensitization are those that are found in high concentrations in a particular area. Thus, in searching for causative and precipitating factors for asthma in an elderly population, sensitization to common aeroallergens should not be overlooked, and allergen avoidance should be part of the management plan in those found to be sensitized.

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